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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/529,447
Filing Date: December 12, 2005
Appellant(s): GYLLENSTEN ET AL.

Holly D. Kozlowski
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed July 27, 2009 appealing from the Office action mailed October 27, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

2002/0137021	Kroeger	09-2002
6,228,368	Gissmann	05-2001

Seedorf et al. “Identification of early proteins of the human papilloma viruses type 16 (HPV 16) and type 18 (HPV 18) in cervical carcinoma cells” EMBO Jour. Vol. 6, No. 1 (1987), pp. 139-144.

Sastre-Garau et al. “Distinct patterns of alteration of myc genes associated with integration of human papillomavirus type 16 or type 45 DNA in two genital tumours” J. General Virology Vol. 81 (2000), pp. 1983-1993.

Sastre-Garau et al. GenBank Accession No. AJ242956 (2000).

Goldsborough et al. GenBank Accession No. J04353 (1994).

Yoo et al. “Hydroxymethylbilane synthase: complete genomic sequence and amplifiable polymorphisms in the human gene" Genomics Vol. 15 (1993), pp. 21-29.

Yoo et al. GenBank Accession No. M95623 (1993).

Swan et al. “ A sensitive, type-specific, fluorogenic probe assay for detection of human papillomavirus DNA” J. Clin. Microbiol. Vol. 35, No. 4 (1997), pp. 886-891.

Buck et al. “Design strategies and performance of custom DNA sequencing primers” BioTechniques Vol. 27, No. 3 (1999), pp. 528-536.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 9 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kroeger et al. (U.S. Patent Pub. No. 2002/0137021) in view of Gissmann et al. (U.S. Patent No. 6,228,368) and further in view of Goldsborough et al. (GenBank Accession No. J04353, 1994) and further in view of Seedorf et al. (EMBO J. (1987) 6:139-144) and further in view of Sastre-Garau et al. (J. Gen. Virol. (2000) 81:1983-1993 and GenBank Accession No. AJ242956) and further in view of Buck et al. (BioTechniques (1999) 27:528-536).

With regard to claims 9 and 21, Kroeger teaches a kit for detecting oncogenic HPV, including HPV 16, 18, 31 and 45 (see Table 1 on p. 2), the kit comprising primers and probes that can be used in a cocktail for amplification and detection of multiple HPV types at once (paragraph 6, lines 1-12, paragraph 7, lines 1-26 and paragraph 24, lines 1-8).

Kroeger does not teach a kit comprising the amplification primers of SEQ ID NOS: 1-8, and the probes of SEQ ID NOS: 21-24, for detection of HPV 16, 18, 31, 35 and 45, wherein the primers and probes specific for HPV 16 detect a sequence in the E7 open reading frame, the primers and probes specific for HPV 18 and 45 detect a sequence in the E1 open reading frame, and the primers and probes specific for HPV 31 detect a sequence in the E6 open reading frame.

With regard to claim 9, Gissmann teaches a sequence within the E7 open reading frame of HPV 16 that can be used for designing primers SEQ ID NO: 1 and SEQ ID NO: 2, and the probe SEQ ID NO: 21 for detection and quantification of HPV 16 (positions 91-111 of SEQ ID NO: 3 of Gissmann is homologous to SEQ ID NO: 1, positions 168-146 of SEQ ID NO: 3 of Gissmann is homologous to SEQ ID NO: 2, and positions 121-142 of SEQ ID NO: 3 of Gissmann is homologous to SEQ ID NO: 21).

With regard to claim 9, Goldsborough teaches a sequence within the E6 open reading frame of HPV 31 that can be used for designing primers SEQ ID NO: 3 and SEQ ID NO: 4 and the probe SEQ ID NO: 22 for detection and quantification of HPV 31 (positions 476-497 of J04353 of Goldsborough is homologous to SEQ ID NO. 3, positions 556-533 of J04353 is homologous to SEQ ID NO: 4, and positions 529-507 of J04353 is homologous to SEQ ID NO: 22).

With regard to claim 9, Seedorf teaches a sequence within the E1 open reading frame of HPV 18 that can be used for designing primers SEQ ID NO: 5-7 and the probe SEQ ID NO: 23 and 24 for detection and quantification of HPV 18 (positions 1093-1113

of Seedorf, Figure 1a is homologous to SEQ ID NO: 5/6, positions 1168-1148 is homologous to SEQ ID NO: 7, and positions 1115-1140 is homologous to SEQ ID NO: 23/24).

With regard to claim 9, Sastre-Garau teaches a sequence within the E1 open reading frame of HPV 45 that can be used for designing primer SEQ ID NO: 8 for detection and quantification of HPV 45 (positions 7185-7164 of AJ242956 of Sastre-Garau is homologous to SEQ ID NO: 8).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to utilize the sequences taught by Gissmann, Goldsborough, Seedorf and Sastre-Garau in order to design amplification primers and probes for a kit to detect and quantify HPV in a type-specific manner, as taught by Kroeger. Thus, an ordinary practitioner would have been motivated to use such sequences in order to design primers and probes that are specific for particular HPV types, especially high-risk types such as HPV 16, 18, 31 and 45 associated with cervical cancer. Such a kit provides the necessary primers, probes and other amplification reagents to form cocktails that can detect multiple HPV types in a single amplification reaction (Kroeger, paragraph 7, lines 11-23 and paragraph 24, lines 1-8).

In the recent court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding "obvious to try", the Court stated: "A person of ordinary skill is also a person of ordinary creativity, not an automaton.

The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Gissmann, Goldsborough, Seedorf and Sastre-Garau, which are 100% derived from sequences expressly suggested by the prior art of Gissmann, Goldsborough, Seedorf and Sastre-Garau as useful for primers for the detection and quantification of human papillomavirus, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

5. Claims 10, 11, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kroeger et al. (U.S. Patent Pub. No. 2002/0137021) in view of Gissmann et al. (U.S. Patent No. 6,228,368) and further in view of Goldsborough et al.

(GenBank Accession No. J04353, 1994) and further in view of Seedorf et al. (EMBO J. (1987) 6:139-144) and further in view of Sastre-Garau et al. (J. Gen. Virol. (2000) 81:1983-1993 and GenBank Accession No. AJ242956) and further in view of Buck et al. (BioTechniques (1999) 27:528-536) as applied to claim 9 above, and further in view of Yoo et al. (Genomics (1993) 15:21-29 and GenBank Accession No. M95623).

Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck together teach the limitations of claims 9 and 21 as discussed above.

Neither Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau nor Buck teach amplification primers SEQ ID NO:19 and SEQ ID NO:20 and the probe SEQ ID NO:30, for detection and quantification of the amount of the human single copy gene hydroxymethylbilane synthase (HUMPBGDA).

With regard to claims 10, 11, 22 and 23, Yoo teaches a sequence that can be used for designing primers SEQ ID NO:19 and SEQ ID NO:20, and the probe SEQ ID NO:30 for detection and quantification of the human single copy gene HUMPBGDA (positions 4750-4770 of the PBGD sequence taught by Yoo is homologous to SEQ ID NO. 19, positions 4868-4850 of Yoo is homologous to SEQ ID NO. 20, and positions 4788-4813 of Yoo is homologous to SEQ ID NO. 30).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to include in the kit taught by Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck, the additional sequences taught by Yoo in order to design amplification primers and probes for the kit to detect and quantitate HUMPBGDA, used as a reference gene for quantification purposes. Thus,

an ordinary practitioner would have been motivated to use such sequences in order to design primers and probes that are specific for a single-copy human PBGD gene which can be used for determining cell-copy number for more accurate detection and quantification of human papillomavirus such as the high-risk types of HPV 16, 18, 31 and 45 associated with cervical cancer.

In the recent court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding "obvious to try", the Court stated:

"A person of ordinary skill is also a person of ordinary creativity, not an automaton. The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoo, which are 100% derived from sequences expressly suggested by the prior art of Yoo as useful for primers for the detection and quantification of human PBGD and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected

according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

6. Claims 12, 14, 24 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kroeger et al. (U.S. Patent Pub. No. 2002/0137021) in view of Gissmann et al. (U.S. Patent No. 6,228,368) and further in view of Goldsborough et al. (GenBank Accession No. J04353, 1994) and further in view of Seedorf et al. (EMBO J. (1987) 6:139-144) and further in view of Sastre-Garau et al. (J. Gen. Virol. (2000) 81:1983-1993 and GenBank Accession No. AJ242956) further in view of Buck et al. (BioTechniques (1999) 27:528-536) as applied to claim 9 above, and further in view of Swan et al. (J. Clin. Microbiol. (1997) 35:886-891).

Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck together teach the limitations of claims 9 and 21 as discussed above.

Neither Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau nor Buck teach a kit comprising at least two different fluorophores for detection and diagnosis of cervical cancer.

With regard to claims 12, 14, 24 and 26, Swan teaches a type-specific fluorogenic probe assay for detection and quantification of HPV, including high-risk types associated with cervical cancer, using probes containing FAM or HEX and a

rhodamine quencher dye, TAMRA (p. 886, column 1, lines 1-5, lines and column 2, lines 7-25).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck that disclose sequences to allow designing of primers and probes for a kit for detection and quantification of HPV 16, 18, 31 and 45 with those of Swan that teach the use of fluorogenic probes for detecting and quantifying high-risk HPV types since the probes can all be readily prepared with fluorescent labels during synthesis using the necessary phoshoramidites and esters (Swan, p. 886, column 2, lines 16-25). Thus, an ordinary practitioner would have been motivated to use HPV sequences in order to design primers and fluorescently-labeled probes to provide a kit for performing a fast, simple and highly sensitive detection method for typing HPV DNA, since the probe is present in the PCR reaction mixture to allow direct measurement of fluorescence after PCR without further manipulations (Swan, p. 890, column 1, line 13 to column 2, line 5).

7. Claims 13, 18-20 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kroeger et al. (U.S. Patent Pub. No. 2002/0137021) in view of Gissmann et al. (U.S. Patent No. 6,228,368) and further in view of Goldsborough et al. (GenBank Accession No. J04353, 1994) and further in view of Seedorf et al. (EMBO J. (1987) 6:139-144) and further in view of Sastre-Garau et al. (J. Gen. Virol. (2000) 81:1983-1993 and GenBank Accession No. AJ242956) and further in view of Buck et al.

(BioTechniques (1999) 27:528-536) and further in view of Yoo et al. (Genomics (1993) 15:21-29 and GenBank Accession No. M95623) as applied to claims 10 and 11 above, and further in view of Swan et al. (J. Clin. Microbiol. (1997) 35:886-891).

Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck and Yoo together teach the limitations of claims 10, 11, 22 and 23 as discussed above.

Neither Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck nor Yoo teach a kit comprising three different fluorophores for detection and diagnosis of cervical cancer.

With regard to claims 13, 18-20 and 25, Swan teaches a type-specific fluorogenic probe assay for detection and quantification of HPV, including high-risk types associated with cervical cancer, using probes containing FAM or HEX and a rhodamine quencher dye, TAMRA (p. 886, column 1, lines 1-5, lines and column 2, lines 7-25).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck and Yoo that teach sequences to allow designing of primers and probes for a kit for detection and quantification of HPV 16, 18, 31 or 45 as well as that of a house-keeping gene, PBGD, with those of Swan that teach the use of fluorogenic probes for detecting and quantifying high-risk HPV types since the HPV and PBGD probes can all be readily prepared with fluorescent labels during synthesis using the necessary phoshoramidites and esters (Swan, p. 886, column 2, lines 16-25). Thus, an ordinary practitioner would have been motivated to use HPV and PBGD sequences in order to design primers and fluorescently-labeled probes to provide

a kit for performing a fast, simple and highly sensitive detect method for typing HPV DNA, since the probe is present in the PCR reaction mixture to allow direct measurement of fluorescence after PCR without further manipulations (Swan, p. 890, column 1, line 13 to column 2, line 5). Furthermore, primers and a probe for a housekeeping gene such as PBGD or β-globin (used by Swan) can be used to normalize the HPV signal to improve quantification, since this allows samples with unequal DNA content or reaction inhibitors to be measured accurately (Swan, p. 890, column 2, lines 28-36).

(10) Response to Argument

Introduction

This application involves one central 35 U.S.C. 103(a) rejection of two base claims and depends upon whether all of the claim elements are taught by the combination of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck and whether there is motivation to combine the references, particularly with regard to the limitations for primer and probe sequences. The remaining claims are rejected by the above references and further in view of Yoo, further in view of Swan, or further in view of Yoo and Swan.

Issue 1 – Does the combination of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck render the claims *prima facie* obvious?

Legal Standard

The legal standard for obviousness is based upon the factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

***Prima Facie* Case**

The *prima facie* case of obviousness is set forth in the rejection given above. The first issue is whether the combined references teach each of the limitations of the claims, particularly with regard to the limitations for primer and probe sequences.

Claim 9

Appellant argues that the combined teachings of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck fail to disclose or suggest the primers and probes of a kit useful for balanced co-amplification of different HPV types in a mixed sample and to avoid hindrances to an efficient PCR. In particular, Appellant argues that the primers and probes, as described in the present specification, are selected so as not to compete during amplification and detection, and therefore provides a significant advantage in the ability to quantify individual HPV types in mixed infections. Appellant then argues that the primary reference of Kroeger, while teaching a cocktail of probes for detecting multiple HPV types at once, fails to disclose or suggest the specific combination of probes and primers recited in claim 9. Appellant argues that

Kroeger teaches away from this specific combination of probes and primers by requiring probes that hybridize within a 140-bp region of the L1 gene for detection of specific HPV types. Appellant further argues the deficiencies of Kroeger are not resolved by the secondary references of Gissmann, Goldsborough, Seedorf and Sastre-Garau, which teach sequences that are homologous to one or more of the claimed primers or probes, but fail to teach the specific primers of SEQ ID NOS: 1-8 and the specific probes of SEQ ID NOS: 21-24 cited in claim 9.

The Examiner relied on Kroeger as the primary reference since this reference teaches multiplexed detection of multiple HPV types using a cocktail of multiple probes specific for unique regions within the L1 gene (paragraphs 7 and 23), as well as detection in separate reactions (paragraph 37). Though Kroeger does not teach any of the specific primers or probes cited in claim 9, the reference does teach a single primer set that is capable of amplifying multiple HPV types, as well as multiple probes that are specific to detection of the different HPV types. Appellant argues that the kit comprising the primers and probes cited in claim 9 provide a significant advantage in the ability to quantify individual HPV types in mixed infections. However, there is no evidence provided that the use of such a kit provides unexpected or superior results for detection of multiple HPV types relative to the prior art such as that taught by Kroeger. In both cases, the kit of the present invention and that of Kroeger provides primers and probes that are used for simultaneous detection of multiple HPV types in a single PCR reaction under standard cycling conditions. Furthermore, though Gissmann, Goldsborough, Seedorf and Sastre-Garau fail to teach the specific primers or probes cited in claim 9,

each reference teaches a sequence from which one of skill in the art would be able to design a gene-specific primer and probe set for detection of a specific HPV type, each set of which could also be combined into a kit according to Kroeger to form a single reaction mixture for simultaneous detection, or to form separate reaction mixtures, since the claim does not require their use in a multiplexed amplification format.

Claim 21

Claim 21 cites forward and reverse primers and probes specific to various HPV genes and types, but does not cite the specific SEQ ID NOS as in claim 9. Appellant argues that the combined teachings of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck also fail to disclose or suggest the forward and reverse primers and probes of a kit useful for detection and quantification of different HPV types in a mixed sample that are specific to different HPV genes, specifically E7 (HPV 16), E1 (HPV 18 and 45) and E6 (HPV 31). Appellant then argues that the primary reference of Kroeger, while teaching a cocktail of probes for detecting multiple HPV types at once, fails to disclose or suggest the specific combination of probes and primers recited in claim 21 directed to different HPV genes for each HPV type. Similarly, Appellant argues that Gissmann, Goldsborough, Seedorf and Sastre-Garau fail to make up for the deficiencies of Kroeger since, even though each teaches a sequence homologous to the cited HPV genes, they fail to teach a combination of primers and probes having the functionality required by claim 21.

The Examiner also relied on Kroeger as the primary reference for claim 21 since this reference teaches detection of multiple HPV types, even though only one gene (L1)

is targeted by the single set of primers and the cocktail of multiple probes. However, the secondary references of Gissmann, Goldsborough, Seedorf and Sastre-Garau each teach a sequence homologous to the cited HPV genes, and even though these references are not directed to detection and quantification of HPV, there is no functionality connected to the primers and probes cited in claim 21, only that they are directed to a particular HPV gene and type. Therefore, based on the known sequence, one of skill in the art would be able to design a gene-specific primer and probe set for detection of a specific HPV type, each set of which could also be combined into a kit according to Kroeger to form a single reaction mixture for simultaneous detection, or to form separate reaction mixtures, since the claim does not require their use in a multiplexed amplification format.

Motivation to combine

The Federal Circuit has recently provided a detailed explanation of the subsidiary requirement for motivation to combine in Dystar v. Patrick Co., 80 USPQ 2d 1641, 1651(Fed. Cir. 2006) noting,

> "Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references."

The Dystar court clarifies that motivation exists when the improvement results in a more desirable process and the issue then devolves to whether the ordinary artisan possesses the knowledge capable of combining the references. Here, where the ordinary practitioner is a Ph.D. with several years experience, there is no doubt that the ordinary artisan possesses the knowledge and motivation sufficient to prepare DNA fragments by homopolymer tailing for purposes of attaching adapters. Some of the listed motivations of Dystar, to result in a cleaner, more efficient, faster, cheaper and more durable assay, would motivate the ordinary practitioner to perform fragment labeling and adapter attachment in a more efficient manner.

Appellant argues that the Examiner has failed to indicate how one of ordinary skill in the art would be motivated to provide a kit for detection of different HPV types comprising probes and primers which amplify different HPV genes, counter to the primary reference of Kroeger which teaches amplification and detection of a single gene. Furthermore, Appellant argues that there is also no motivation in any of the cited secondary references to provide the specific combination of primers cited in claims 9 and 21, particularly to obtain the functionality of balanced and specific amplification without competition among the primers. Kroeger has provided a kit for use in detection of multiple HPV types after amplification using a single primer pair, with detection performed either in multiplex or separate reactions using type-specific probes. Since Kroeger teaches a kit that can be used for detection of multiple HPV types, an ordinary practitioner would have been motivated to design alternative primer and probe sets based on other known HPV sequences. Though Gissmann, Goldsborough, Seedorf

and Sastre-Garau are not directed to detection and quantification of HPV, Kroeger provides a general guidance to one of ordinary skill in the art to design and use primers and probes for diagnostic applications such as detection of HPV types by PCR (see paragraphs 14-17). The ordinary practitioner will recognize that target sequences are not limited to those taught only by Kroeger, but rather any known HPV sequence may be targeted using primer and probe design tools well-known in the art at the time of the invention.

Appellant then argues that the Examiner relies on the court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), in which the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103(a). Appellant argues that situations regarding a combination which is obvious to try when there are a finite number of identified, predictable solutions may be obvious under § 103(a), but would not be obvious in the current case where an almost infinite number of sequences could be selected from the teachings of Gissmann, Goldsborough, Seedorf and Sastre-Garau. However, these references teach a very limited number of specific HPV sequences, those coding for sequences within the E1, E6 and E7 of HPV 18, 45, 16 and 31. Though a large number of potential primers and probes could be designed for each target, primer and probe design tools available to the ordinary practitioner at the time of the invention are designed to select sequences within a given target that are most likely to succeed in PCR, including real-time PCR. Furthermore, in a recent Board decision, the "obvious to try" test was deemed

particularly relevant with regard to nucleotide sequences, as summarized by the Board in Ex parte Kubin, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007):

"General rule that it is improper to use prior art disclosure of particular protein, together with methods of isolating cDNA disclosed in other references, to reject claims drawn to specific nucleotide sequences on ground of obviousness is not viable to extent it rejects "obvious to try" test, since "obvious to try" may be appropriate test in more situations than previously contemplated; in present case, rule does not preclude finding that claimed nucleotide sequences encoding natural killer cell activation inducing ligand ("NAIL") polypeptide would have been obvious to person of ordinary skill in art based on prior art patent's disclosure of "p38" protein, which is same protein as NAIL, and patent's express teachings on how to isolate p38 cDNA by conventional techniques, since "problem" facing persons in art was isolation of NAIL cDNA, and there were limited number of methodologies for doing so, since skilled artisan would have had reason to try these methodologies with reasonable expectation that at least one would be successful, and since isolating NAIL cDNA thus was product ordinary skill and common sense, not innovation."

The Board emphasizes that the "obvious to try" test may be an appropriate test in more situations than previously contemplated, and is now considered more relevant with regard to claimed polynucleotides than *In re Deuel*.

Based on our findings and those of the Examiner, at least one of Appellants' claimed polynucleotides would have been obvious to one of ordinary skill in the art at the time Appellants' invention was made. Regardless of some factual similarities between Deuel and this case, Deuel is not controlling and thus does not stand in the way of our conclusion, given the increased level of skill in the art and the factual differences. See In re Wallach, 378 F.3d 1330, 1334, 71 USPQ2d 1939, 1942 (Fed. Cir. 2004) ("state of the art has developed [since] In re Deuel").

Appellants heavily rely on Deuel. (See, e.g., Br. 19.) To the extent Deuel is considered relevant to this case, we note the Supreme Court recently cast doubt on the viability of Deuel to the extent the Federal Circuit rejected an "obvious to try" test. See KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, ___, 82 USPQ2d 1385, 1394, 1396 (2007) (citing Deuel, 51 F.3d at 1559). Under KSR, it's now apparent "obvious to try" may be an appropriate test in more situations than we previously contemplated. When there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007). This reasoning is applicable here. The "problem" facing those in the art was to isolate NAIL cDNA, and there were a limited number of methodologies available to do so. The skilled artisan would have had reason to try these methodologies with the reasonable expectation that at least one would be successful. Thus, isolating NAIL cDNA was "the product not of innovation but of ordinary skill and common sense," leading us to conclude NAIL cDNA is not patentable as it would have been obvious to isolate it.

Thus, since the claimed primers and probe simply represent structural homologs of the sequences taught by Gissmann, Goldsborough, Seedorf and Sastre-Garau, which are 100% derived from sequences of HPV, the claimed primers are *prima facie*

obvious over the cited references in the absence of secondary considerations. As discussed above, there is no evidence provided that the use of the kit as claimed provides unexpected or superior results for detection of multiple HPV types relative to the prior art such as that taught by Kroeger. In both cases, the kit of the present invention and that of Kroeger provide primers and probes that are used for simultaneous detection of multiple HPV types in a single PCR reaction under standard cycling conditions. In the specification, real-time PCR reactions are described that are performed over 40-50 cycles using a two-step procedure (page 7). The sensitivity, specificity and reproducibility of typical assay results are described, including those obtained using clinical samples with mixed infections, where initial viral copies are detected in the range of 1,000 to 100,000 copies (pages 10-14). However, there is no attempt to compare such results with other multi-analyte HPV tests available at the time of the invention. Kroeger describes such a test, based on PCR amplification using 40 cycles, with sensitivities in the range of 1,000 to 10,000, depending on the HPV type (paragraph 35 and Table 2). Thus, there is no evidence that using a kit comprising the claimed primers and probes results in unexpected or superior results relative to the known art at the time of the invention.

Appellant then argues that the Examiner places undue emphasis on the equivalence of primers as supported by Buck, arguing that the teachings of Buck do not apply to all primers in all amplification reactions, since Buck only discloses amplification of a single test nucleic acid. With regard to the issue of equivalence of the primers, MPEP 2144.06 notes, “Substituting equivalents known for the same purpose. In order

to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)." While the Appellant is correct in stating that Buck used a highly pure template for testing primers under optimal sequencing conditions, the evidence set forth by Buck still provides an ordinary practitioner with a reasonable expectation of success for successful amplification of a known sequence in an impure sample, after initially identifying candidate primers. As previously stated, Kroeger provides the necessary guidance to one of ordinary skill in the art for the design of primers and probes for detection of HPV types by PCR.

Therefore, the rejections using Kroeger in view of Gissmann and further in view of Goldsborough, Seedorf, Sastre-Garau and Buck teach or suggest all the elements of the claims and provide a proper motivation as required by the Federal Circuit and these rejections should be sustained.

Issue 2 – Does the combination of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck and Yoo render claims 10, 11, 22 and 23 *prima facie* obvious?

Appellant argues that claims 10, 11, 22 and 23 should be reversed since the deficiencies of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck, which prevent the combination of the cited references from rendering the kits of base

claims 9 and 21 obvious, are not resolved by the teachings of Yoo of a sequence for the human single copy gene HUMPBGDA. Appellant argues that Yoo does not teach the combination of primers and probes related to a kit for detection and quantification of HPV, and furthermore does not teach the combination of primers and probes related to a kit for detection and quantification of human single copy gene, or that such a combination would be useful to normalize HPV detection results. Appellant further argues that the teaching by Yoo of a sequence of a human single copy gene does not render primers and a probe obvious for inclusion in the kits of the present claims for measuring individual HPV types. As discussed above, the primers and probes cited in the kit are prima facie obvious over the combination of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck. Though Kroeger does not teach any of the specific primers or probes cited in claim 9, the reference teaches a combination of a primer and multiple probes that are specific to detection of the different HPV types. Furthermore, for purposes of establishing the sensitivity of HPV testing by PCR, Kroeger teaches the use of M13 plasmids as controls for quantifying HPV plasmids by establishing a standard curve (paragraph 32). For quantitative analysis of clinical samples, the ordinary practitioner will recognize that an *in vivo* control is required, such as a housekeeping gene of known copy number. Yoo teaches such as a gene, including the entire complete genomic sequence (p. 21, column 2, lines 13 and GenBank Accession number M95623), from which one of skill in the art would be able to design a gene-specific primer and probe set for detection and quantification.

As above, Appellant then argues that the Examiner relies on the court decision

KSR International Co. v. Teleflex Inc., 82 127 SCt 1727 (2007), in which the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103(a). Appellant argues that situations regarding a combination which is obvious to try when there are a finite number of identified, predictable solutions may be obvious under § 103(a), but would not be obvious in the current case where an almost infinite number of sequences could be selected from the teachings of Yoo. However, this reference teaches a single sequence of a human gene, that coding for the HUMPBGDA gene. Though a large number of potential primers and probes could be designed for such a target, primer and probe design tools available to the ordinary practitioner at the time of the invention select sequences within a given target that are most likely to succeed in PCR. In light of the court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), as well as the recent Board decision, as summarized by the Board in Ex parte Kubin, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007), since the claimed primers and probe simply represent structural homologs of the sequences taught by Yoo, which are 100% derived from sequences of the HUMPBGDA gene, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations. As discussed above, there is no evidence provided that the use of the kit as claimed, including the primers and probes for the HUMPBGDA gene, provides unexpected or superior results for detection of multiple HPV types relative to the prior art such as that taught by Kroeger.

Therefore, the rejections using Kroeger in view of Gissmann and further in view of Goldsborough, Seedorf, Sastre-Garau, Buck and Yoo teach or suggest all the elements of the claims and provide a proper motivation as required by the Federal Circuit and these rejections should be sustained.

Issue 3 – Does the combination of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck and Swan render claims 12, 14, 24 and 26 *prima facie* obvious?

Appellant argues that claims 12, 14, 24 and 26 should be reversed since the deficiencies of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck, which prevent the combination of the cited references from rendering the kits of base claims 9 and 21 obvious, are not resolved by the teachings of Swan of a preparation and use of probes in a fluorogenic probe assay for detection of HPV. Appellant argues that Swan does not teach the combination of primers and probes related to a kit for detection and quantification of HPV, and furthermore teaches, similar to Kroeger, probes directed to a single gene, L1, for detection of various HPV types, instead of the primers and probes directed to different HPV reading frames of the instant invention. Appellant further argues some of the probes taught by Swan display cross reactivity when detecting as few as 2000 copies of HPV-16 and HPV-51, which would be avoided when using the primer and probes cited in claim 9.

Swan describes a highly sensitive, type-specific test for several HPV types based on the use of fluorogenic probes, and demonstrates detection of less than 100 copies of HPV DNA in human cervical specimens for five different HPV probes in control

experiments (p. 887, column 2, line 25 to p. 888, column 1, line 2 and Figure 3) as well as in the analysis of patient samples (p. 888, lines 7-16 and Figure 4A). Furthermore, the degree of cross-reactivity was low for all of the assays, requiring at least 2000 copies of a heterologous probe to generate a signal equivalent to detecting 30 copies of HPV-33, for example (p. 888, column 1, lines 2-6). Thus, there is no evidence provided that the use of the kit as claimed, including the primers and probes comprising at least two different fluorophores, provides unexpected or superior results for detection of multiple HPV types relative to the prior art such as that taught by Kroeger or Swan.

Therefore, the rejections using Kroeger in view of Gissmann and further in view of Goldsborough, Seedorf, Sastre-Garau, Buck and Swan teach or suggest all the elements of the claims and provide a proper motivation as required by the Federal Circuit and these rejections should be sustained.

Issue 4 – Does the combination of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck, Yoo and Swan render claims 13, 18-20 and 25 *prima facie* obvious?

Appellant argues that claims 13, 18-20 and 25 should be reversed since the deficiencies of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau and Buck, which prevent the combination of the cited references from rendering the kits of independent claims 9 and 21 obvious and the deficiencies of Kroeger, Gissmann, Goldsborough, Seedorf, Sastre-Garau, Buck and Yoo, which prevent the combination of the cited references from rendering the kits of claims 10, 11 and 22 obvious, from which claims 13, 18-20 and 25 are directly dependent, are not resolved by the teachings of

Swan. Though Swan teaches the preparation and use of probes in a fluorogenic probe assay for detection of HPV, Appellant argues that Swan does not teach the combination of primers and probes related to a kit for detection and quantification of HPV, and furthermore teaches, similar to Kroeger, probes directed to a single gene, L1, for detection of various HPV types, instead of the primers and probes directed to different HPV reading frames of the instant invention. Appellant further argues some of the probes taught by Swan display cross reactivity when detecting as few as 2000 copies of HPV-16 and HPV-51, which would be avoided when using the primer and probes cited in claim 9.

Swan describes a highly sensitive, type-specific test for several HPV types based on the use of fluorogenic probes, and demonstrates detection of less than 100 copies of HPV DNA in human cervical specimens for five different HPV probes in control experiments (p. 887, column 2, line 25 to p. 888, column 1, line 2 and Figure 3) as well as in the analysis of patient samples (p. 888, lines 7-16 and Figure 4A). Furthermore, the degree of cross-reactivity was low for all of the assays, requiring at least 2000 copies of a heterologous probe to generate a signal equivalent to detecting 30 copies of HPV-33, for example (p. 888, column 1, lines 2-6). Thus, there is no evidence provided that the use of the kit as claimed, including the primers and probes comprising at least three different fluorophores, provides unexpected or superior results for detection of multiple HPV types relative to the prior art such as that taught by Kroeger or Swan.

Therefore, the rejections using Kroeger in view of Gissmann and further in view of Goldsborough, Seedorf, Sastre-Garau, Buck, Yoo and Swan teach or suggest all the

elements of the claims and provide a proper motivation as required by the Federal Circuit and these rejections should be sustained.

(11) Related Proceedings Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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